2. Rejections under 35 U.S.C. § 101

The Examiner rejects claims 1-27 and 35-38 under 35 U.S.C. § 101 on the grounds that the claimed invention is not supported by either a specific and/or substantial asserted utility or a well-established utility. Specifically, the Examiner states that "[t]he claimed library of yeast expression vectors encoding a library of fusion proteins and library of transformed yeast cells, is not supported by a specific asserted utility and doe not, without further research and experimentation, provide an immediate benefit to the public". Applicants respectfully traverse the Examiner's grounds for utility rejection as being improper and unsupported.

Under the "Revised Interim Utility Guidelines" of the PTO, if at least one specific, credible, and substantial utility is provided, a rejection under 35 U.S.C. § 101 should not be made.

1) Specific Utility Provided

The claimed invention provides a diverse library of yeast expression vectors which are designed to be used in an efficient method for high throughput screening of a diverse protein library against a specific target protein, also described in the application. Applicants submit that the utility of the claimed yeast expression vector library derives itself from the screening method with which it may be used.

Classes and highly specific examples of target proteins may be used in the high throughput screening method including epidermal growth factors (EGFs), transferrin, insulin-like growth factor, transforming growth factors (TGFs), interleukin-1, and interleukin-2 are provided in the Specification (See pp. 44-48, "The Target Proteins and Peptides"). Each target protein listed can be used in the claimed method for screening against the protein library. It is taught that the protein library may be a single-chain antibody, scFv which typical comprises a V_H domain and a V_L domain in polypeptide linkage. The proteins screened according to the method can be used in diagnostic applications for the target protein and as therapeutics for a specific disease associated with the target protein.

As taught in the Specification, antibodies identified through the method against a cell surface protein or receptor such as platelet glycoprotein IIb/IIIa receptor can be used to treat coronary artery disease. Antibodies identified through the method against CD4, CAMPATH-1 can be used to treat autoimmune diseases. See Specification, page 45, last paragraph. The myriad of specific utilities provided by the method of the present invention is endless.

To further demonstrate that a specific asserted utility has been provided, the Examiner's attention is drawn to original dependent claims 21-23 which recite specific disease associated proteins as target proteins. As can be seen from the originally claimed method, at least one

specific utility has clearly been provided.

2) Substantial Utility Provided

A "substantial utility" is defined by the PTO Training Materials for the "Revised Interim Utility Guidelines" as a "real world" use. An assay method for identifying compounds that themselves have a "substantial utility" is considered to be a "real world" use. The library designed for use in that assay method would likewise have "real world" use.

As discussed above, the claimed library may be used in a high throughput assay for screening proteins such as therapeutic antibodies that can bind to specific disease-associated proteins. The resulting screened proteins can be used in diagnostic applications and for treating specific diseases in the clinic. Applicants therefore submit that a "real world" use demonstrating a substantial utility has also been provided.

3) Credible Utility Provided

The claimed library also has credible utility. It is well known that antibodies are widely used for the diagnosis and treatment of disease, the most celebrated one being HERCEPTIN® (Genentech Inc.) which has been shown to have substantial utility in treating breast cancer. Many commercial entities such as Cambridge Antibody Therapeutics use various screening methods such as phage display to select for therapeutic antibodies. The claimed library's use in a high throughput assay for screening compounds such as therapeutic antibodies that can bind to specific disease associated proteins would be readily recognized to have credible utility as an alternative to phage display and other such screening methods for selecting therapeutic antibodies. Applicants therefore submit that a credible utility has also been provided.

In view of the specific, credible, and substantial utility of the claimed method, the pending utility rejection should be withdrawn.

3. Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner rejects claims 1-27 and 35-38 under 35 U.S.C. § 112, First Paragraph for insufficient written description and lack of enablement. The grounds for the Examiner's rejection are based on those for the rejection under 35 U.S.C. § 101. Specifically, the Examiner states that "since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention".

As discussed in Section 2 above, the Examiner's rejection under 35 U.S.C. § 101 is improper and unsupported and should be withdrawn. Given that the pending utility rejection is unsupported, the utility rejection cannot support the pending rejection under 35 U.S.C. § 112, First Paragraph. For this reason, Applicants respectfully request that the rejection under 35 U.S.C. § 112, First Paragraph be withdrawn.

4. Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner rejects claims 10-13, 20 and 21 under 35 U.S.C. § 112, Second Paragraph for being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants address each of the indefiniteness rejections in detail below.

1) Claims 10-12

Applicants' cancellation of claims 10-12 renders the rejection under 35 U.S.C. § 112, Second Paragraph moot.

2) Claim 13 "Multimeric Proteins"

The Examiner rejects claim 13 for being indefinite on the grounds that it is not clear how the sequence of a single multimeric protein can vary within a library of a plurality of multimeric proteins. Applicants amend claim 13 to specify that "the library of fusion proteins encode a class of multimeric proteins and the first and the second polypeptide subunits are subunits of a multimeric protein in the class". Withdrawal of the rejection under 35 U.S.C. § 112, Second Paragraph is therefore respectfully requested.

3) Claims 20 and 21

Applicants' cancellation of claims 20 and 21 renders the rejection under 35 U.S.C. § 112, Second Paragraph moot.

5. Rejection under 35 U.S.C. § 102

1) Hoeffler et al.

Claims 1-21, 25-27, and 35-38 are rejected under 35 U.S.C. § 102(a) in view of Hoeffler et al. (1999, WO 99/28502). Specifically, the Examiner states that this reference teaches libraries of yeast expression vectors encoding single chain fragments of immunoglobulin variable domains V_H and V_L linked by a peptide (sFv).

Independent claim 1, as amended, specifies a highly diverse library of tester proteins each having two variable domains. The diversity of the tester protein library is specified to be at least $1x10^7$. Support for the claim language appears at the Specification at page 28, line 28.

In contrast, the sFv library constructed by Hoeffler et al. has a diversity of $3.6X10^6$. Hoeffler, et al., page 54, lines 5-6. Hoeffler's lower diversity library is insufficient to anticipate the diversity of the claimed library. Withdrawal of the rejection under 35 U.S.C. § 102(a) is therefore respectively requested.

2. Rejection based on Filpula et al.

Claims 1-3, 15-17, 19-24, 26, 35, and 36 are rejected under 35 U.S.C. § 102(b) as being anticipated by Filpula et al. In general, the Examiner's rejection is based on the grounds that this reference teaches "a number of different single chain antibody (SCA) fusion protein yeast expression vectors and yeast transformed with these vectors".

As described above, claim 1 as amended specifies a library of yeast expression vectors encoding a library of tester proteins with a diversity of at least $1x10^7$. Filpula et al. does not teach or suggest a single chain antibody library having a diversity of at least $1x10^7$. Filpula et al. merely teaches how to synthesize single-chain antibody capable of glycosylation. Specifically, amino acids required for glycosylation are specified in various positions of the single-chain antibody. See Filpula, et al., Abstract, and claim 1. Since Filpula, et al. does not teach a library with the diversity of the claimed invention, Filpula et al. fails to anticipate the claims as amended.

6. Rejection under 35 U.S.C. § 103

The Examiner rejects claims 1-27 and 35-38 under 35 U.S.C. § 103(a) as being unpatentable over Hoeffler et al. and Filpula et al. Applicants traverse the Examiner's grounds for rejection for the following reasons.

As discussed above, Hoeffler et al. does not teach a highly diverse library of single chain antibody having a diversity of at least $1x10^7$ as is presently claimed. Instead, Hoeffler, et al. teaches a lower diversity of $3.6X10^6$ and further teaches that that level of diversity is sufficient. Hoeffler's teaching that "[t]he diversity of the library doesn't need to be much above 10^6 since the transformation capacity of yeast is generally 10^7 or below." See Hoeffler, et al., page 54, lines 5-7. This effectively teaches away from the claimed invention.

As also discussed above, Filpula et al. fails to teach a highly diverse library of single chain antibody having a diversity of at least $1x10^7$ as is presently claimed. Filpula, et al. thus fails to remedy the shortfall in the teaching of Hoeffler, et al. Since neither reference teaches

the claimed diversity, the combination of references have insufficient teaching to set forth a prima facie case for obviousness. For this reason, the present rejection for obviousness should be withdrawn.

CONCLUSION

In light of the remarks and arguments set forth above, Applicants earnestly believe that are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

Date: June 27, 2001

By: _____
Shirley Chen, Ph.D.
Registration No. 44,608

WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304-1505
Direct line: (650) 565-3856
Client No. 021971